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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/665,689	09/18/2003	David A. Estell	GC532-C1	6798

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EXAMINER

MOORE, WILLIAM W

ART UNIT	PAPER NUMBER
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1656

DATE MAILED: 11/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/665,689

Applicant(s)

ESTELL, DAVID A.

Examiner

William W. Moore

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 December 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 15-29 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 15-29 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>20030918</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Priority

Applicant's claim in the Declaration of Inventorship and in the amendment to the first page of the specification filed 18 July 2003 to priority of the 15 April 1998 filing date of the parent application No. 09/060,854, of which the instant application is a continuation, is hereby acknowledged.

Information Disclosure Statement

Applicant's Information Disclosure Statement [IDS] filed with the application on 18 September 2003 is hereby acknowledged.

Preliminary Amendment

Applicant's Preliminary Amendments filed with the application on 18 September 2003 have been entered, revising continuing data for the instant application at page 1 of the specification, providing sequence identifiers for, and otherwise revising, descriptions of the Drawing Figures 2, 3A and 3B, 7A-C, and 8A-C, at page 8 of the specification, canceling the original claims 1-14, and adding the new claims 15-29. The amendments add no new matter to the disclosure and the new claims 15-29 conform, in large part, to claims allowed in the parent application serial No. 09/ 060,854, since issued as US Patent No. 6,642,011.

Objection: Lack of Sequence Rules Compliance

Compliance with 37 CFR 1.821 and 1.822 is required in response to this Office action. The Sequence Listing for SEQ ID NO:1, in both the printed sequence listing and the computer readable form of the sequence listing, fails to comply with requirements of for a Sequence Disclosure because the nucleic acid sequence of SEQ ID NO:1 is not accompanied by a presentation of the 382 codons, or the 382 amino acids they encode, in the coding region indicated in the information fields of the Sequence Listing. See, the

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second set of information fields <221> and <222> for SEQ ID NO:1. SEQ ID NO:1 provides the entire precursor subtilisin coding sequence, thus must be separated into codons with the precursor amino acid sequence provided beneath the codons. As noted in the communication mailed in the parent application on 10 October 2001, 37 CFR 1.822(c)(3) requires that "bases in the coding parts of a nucleotide sequence shall be listed as triplets (codons)" and that "amino acids corresponding to the codons in the coding parts of a nucleotide sequence shall be typed immediately below the corresponding codons." In response to this communication, Applicant must supply a corrected Sequence Listing, in both printed and computer-readable forms, presenting SEQ ID NO:1 divided into codons throughout its entire coding sequence, accompanied by the entire encoded amino acid sequence, and accompanied by a Statement that both forms of the Sequence Listing are the same.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 15-29 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 6,642,011. Although the conflicting claims are not identical, they are not patentably distinct from each other because the methods claimed herein are described, nearly verbatim, in the patented claims 1-15 where the only difference arises in step (d) of methods recited in

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the independent, patented, claims 1 and 8 which require replacement with an epitope region from a particular, rather than generic, polypeptide.

Claims 15-29 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2-14 of U.S. Patent No. 6,835,550. Although the conflicting claims are not identical, they are not patentably distinct from each other because the methods claimed herein are embraced by methods of the patented claims 2-14 wherein modification of a protein, which may be a protease, to neutralize a T-cell epitope includes replacing a more immunogenic epitope region with a less immunogenic region of an analogous polypeptide.

Claims 15-29 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 13 and 14 of copending Application No. 10/924,092. Although the conflicting claims are not identical, they are not patentably distinct from each other because methods claimed herein are embraced by methods of the pending claims 13 and 14 of modifying a generic protein, which may be a protease, to neutralize a T-cell epitope by replacing the epitope with a "sequence" that "substantially mimics" "tertiary structur[al] attributes" but produces a lowered "response from T-cells" than the T-cell epitope to be replaced. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-29 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

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reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification teaches, and claims 15-29 require, replacing a peptide region in a first protease, "a naturally-occurring protease having subtilisin activity", with a peptide region from another polypeptide where the "subtilisin activity" of the first protease, a subtilisin, is retained after replacement. Yet the specification as a whole is directed to using structurally corresponding epitope regions of a "human subtilisin", whereof the amino acids sequence of SEQ ID NO:6 is the only disclosed species, that stimulate no more than a baseline proliferative response in naive human CD4+ and CD8+ T-cells and dendritic cells to replace epitope regions in monodomain, microbial, subtilisins that stimulate a proliferative response in naive human CD4+ and CD8+ T-cells and dendritic cells. See. e.g., page 6, lines 23-33, page 7, lines 4-6, Figures 5, 6 and 8 and page 8, lines 15-24, page 10, lines 10-21, page 13, lines 17-19, page 25, lines 24-34, and page 26, lines 10-11. The specification thus fails to exemplify or describe selection of "analogous epitope regions" of generic polypeptides according to claims (d) of claims 15 and 23 with which to replace an epitope region of a monodomain, microbial, subtilisin so that proteolytic activity is retained despite the replacement. The specification describes no other kind of polypeptide that is a suitable source of a replacement epitope, nor does it suggest the structure of any other kind of polypeptide that might be a suitable source of a replacement epitope region that will stimulate no more than a baseline response of naive human CD4+ and CD8+ T-cells and dendritic cells compared to a structurally corresponding, but T-cell proliferation stimulating, epitope region in a monodomain, microbial, subtilisin. Claims 16-22 and 24-29 are included in the rejection because they depend from claims 15 and 23 without themselves identifying any particular, yet analogous, epitope region for replacement of a subtilisin epitope region. "While one does not need to have carried out one's invention before filing a patent application, one

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does need to be able to describe that invention with particularity” to satisfy the description requirement of the first paragraph of 35 U.S.C. § 112. *Fiers v. Revel v. Sugano*, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993). The specification's treatment of the claimed subject matter is considered to be entirely prospective where skilled artisans in the relevant field of immunology could not predict the structures or sources of other polypeptides from which suitable replacement epitope regions not stimulating more than a baseline response of naive human CD4+ and CD8+ T-cells and dendritic cells might be selected that also support the proteolytic activity of a microbial subtilisin wherein a T-cell proliferation stimulating epitope region may advantageously be replaced.

Claims 15-29 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for the replacement of T-cell proliferation stimulating microbial subtilisin epitope regions with corresponding, non-proliferation stimulating, epitope regions of the human protease having the amino acid sequence set forth in SEQ ID NO:6, does not reasonably provide enablement for the replacement of a T-cell proliferation stimulating epitope region of microbial subtilisin with a corresponding, non-proliferation stimulating, epitope region of another polypeptide not structurally related to the human protease having the amino acid sequence set forth in SEQ ID NO:6. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice a method of the invention commensurate in scope with these claims.

Claims 15 and 23 contemplate an arbitrary selection, without regard to underlying, functionally supportive, structures of any peptide region of a generic polypeptide to replace an epitope region in a microbial subtilisin to substantially reduce the proliferative response in naive human CD4+ and CD8+ T-cells and dendritic cells of a native epitope region in a microbial subtilisin requiring replacement because that native epitope stimulates an unwanted, immunogenic, proliferative response in naive human CD4+ and CD8+ T-cells and dendritic cells. This rejection is stated under the first paragraph of the statute because the specification provides no particular, enabling, guidance for a joint solution of the two essential technical problems: (a) replacement of T-cell proliferation stimulatory native epitope regions of a microbial subtilisin with non-T-cell proliferation

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stimulatory epitope regions drawn from unrelated polypeptides and (b) retention of microbial subtilisin endoproteolytic activity in the replacement-modified microbial subtilisin. It is well settled that 35 U.S.C. § 112, first paragraph, requires that a disclosure be sufficiently enabling to allow one of skill in the art to practice the invention as claimed without undue experimentation and that unpredictability in an attempt to practice a claimed invention is a significant factor supporting a rejection under 35 U.S.C. §112, first paragraph, for non-enablement. See, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (discussing factors relevant to enablement). Applying the factors discussed in *Wands* to Applicant's disclosure, it is apparent that:

a) the specification lacks adequate, specific, guidance for selecting functionally appropriate, non-T-cell proliferation stimulating, replacement epitopes for epitope regions residing in the amino acid sequences of microbial subtilisins other than from the human protease amino acid sequence set forth in SEQ ID NO:6,

b) the specification lacks working examples wherein functionally appropriate, non-T-cell proliferation stimulating, replacement epitopes are selected for the replacement of epitope regions residing in the amino acid sequences of microbial subtilisins other than from the human protease amino acid sequence set forth in SEQ ID NO:6,

c) in view of the prior art publications of record herein, the state of the art and level of skill in the art do not support such functionally non-specific replacements, and,

d) unpredictability exists in the art where no block replacements or peptide regions of microbial subtilisins with other peptides have been successfully accomplished for any particular purpose with retention of the proteolytic activity of the subtilisin prior to modification.

Thus the scope of subject matters embraced by practice of methods comprising the generic replacement steps of clauses (d) of claims 15 and 23 wherein the proliferation of naïve human CD4+ and CD8+ is measured according to clause (g) of claims 15 and 23 is unsupported by the present specification except for replacements by epitope regions of the structurally and functionally similar amino acid sequence of SEQ ID NO:6.

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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Claims 15-29 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 15-22 are indefinite because claim 15 recites, twice in clause (a), “naturally-occurring protease having subtilisin activity” and further recites, in clauses (b) and (c), “naturally-occurring protease”. Claims 16 and 18 subject to this rejection also recite “naturally-occurring protease”. The first term is indefinite because the protease knows not whence it came and there are no structural characteristics inherent in “naturally-occurring” proteases that permit the public and the artisan, seeking to ascertain the metes and bounds of the intended subject matter, to distinguish a “naturally-occurring” protease from a protease designed by a person that has not yet been found to also occur in Nature. The second term is also indefinite because the nature of “subtilisin activity” is undefined by the specification and claims, nor is it clear that is intended to indicate solely proteolytic activity”, nor is there any basis with which to distinguish the broad-spectrum endoproteolytic activity of a microbial subtilase from the proteolytic activity of another serine protease. Both terms that occasion this aspect of the rejection are so indistinct as to be meaningless and this aspect of the rejection may best be addressed by amending clauses (a)-(c) of claim 15 and claims 16 and 18 to state a structural basis for identifying a protease having a T-cell epitope to be replaced in a claimed method. Claims 17 and 19-22 are also included in this aspect of the rejection because they do not remedy the ambiguities of claim 15 from which they depend.

Claims 15-29 are indefinite because clauses (d) in both of claims 15 and 23 recite “analogous epitope region” but fail to further define the nature of “analogous”. It is not clear whether the intended analogy is immunogenic similarity, structural similarity, neither, or based on some other kind of similarity. Claims 16-22 and 24-29 are included in this aspect of the rejection because they fail to remedy the ambiguity of claims 15 and 23 from which they depend.

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Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 571.272.0933 and whose FAX number is 571.273.0933. The examiner can normally be reached Monday through Friday between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisory Primary Examiner, Dr. Kathleen Kerr, can be reached at 571.272.0931. The official FAX number for all communications for the organization where this application or proceeding is assigned is 571.273.8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571.272.1600.

William W. Moore
7 November 2005


NASHAAT T. NASHED PHD.
PRIMARY EXAMINER